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Weight Change and the Risk of Late-Onset Breast Cancer in the Original Framingham Cohort

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Abstract: *Objective: Adult weight gain has been associated with a twofold risk of postmenopausal breast cancer. Data are limited regarding whether weight gain at specific periods of marked changes in estrogen- and insulin-related hormones have different risk associations. This study assesses the relation of adult weight change overall and at specific, hormonally relevant times with diagnosis of a first breast cancer after age 55 (late onset). Methods: Framingham study data were used to assess premenopausal (25–44 yr), perimenopausal (45–55 yr), postmenopausal (after 55 yr), and adult lifetime (from 25 yr) weight change in relation to late-onset breast cancer in 2,873 women followed for up to 48 yr, with 206 late-onset breast cancers. Results: Adult lifetime weight gain was associated with an increased risk of late-onset breast cancer (*P *trend = 0.046). Weight gain during specific time periods was not associated with breast cancer. Data suggested a possible decreased risk of breast cancer with weight loss from ages 25 to 44 and 45 to 55 yr (relative risk = 0.4 [0.2–1.2] and 0.5 [0.3–0.9], respectively). Conclusion: These data confirm prior reports of an association between adult lifetime weight gain and increased risk of late-onset breast cancer and support current recommendations to avoid adult weight gain.*

Introduction

Adult weight, height-adjusted body mass, and weight gain have frequently been associated with increased risk of late-onset breast cancer (1–4). Mechanisms proposed to explain this association include the effects of adiposity on elevation of estrogen and insulin levels, including insulin-like growth factor (IGF) (5–7). There is general agreement that estrogen is involved in the etiology of breast cancer, and many, although not all, studies have found serum estrogen levels to be elevated in postmenopausal women with breast cancer or who later developed breast cancer compared with noncancerous women (8–11). More recently, evidence is emerging about the possible role of insulin and IGF in the association between greater weight and breast cancer (6).

Compared with weight or body mass index (BMI), adult weight gain, generally using a baseline weight at age 18 or 25 yr, has more consistently been found to have an association with late-onset or postmenopausal breast cancer risk (2,12–18). Findings of a stronger association with a longer time period of weight gain (13), time since menopause (19), no use of hormone replacement therapy (HRT) (14,15,18,20), former hormone use (21), sum of weight change by decades, and differences between maximum and minimum adult weight (14) have been reported. It has been suggested that weight gain around times of hormonal change, such as menarche, pregnancy, and menopause, especially may influence breast cancer risk (12,15,19,22–24). A review of anthropometry and breast cancer specifically noted the lack of knowledge about the importance of timing of weight gain to breast cancer occurrence (12). The lack of accuracy that results from use of self-reported weight, especially if self-report refers to a weight that occurred at some time in the past, was noted in this review as a significant hindrance to investigations of associations of weight or weight gain at times of hormonal change and breast cancer (12).

This article investigates the effect of adult weight change at premenopausal (ages 25–44), perimenopausal (ages 45–55), and postmenopausal (>55 yr) ages as well as lifetime adult weight change on late-onset breast cancer risk. To our knowledge, the Framingham cohort is the only long-standing cohort in which weight was measured repeatedly over an extended period of time and hence is one of the few cohorts in

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which these associations can be explored with mostly prospectively collected data, thus addressing some of the gaps that have been noted in studies of weight and breast cancer.

Methods

Sample

The Framingham study began in 1948 and included 2,873 women who were 28–62 yr old (25). Participants have been medically examined approximately biennially. Included in the medical exams were health-related questions and anthropometric measurements, with weight measured at each exam. Women who reported a breast cancer that had occurred at any time before their first exam in which their weight was measured and those who had a breast cancer before age 55 at any time during the study (n = 37) were excluded from the study sample. Two hundred six women developed a first breast cancer after age 55 and subsequent to their first weight measurement.

Breast Cancer Event Ascertainment

Events were defined as a first breast cancer diagnosed after the age of 55 (referred to as late onset) and before exam 23, undertaken between 1992 and 1996. Examination of late-onset breast cancer allows examination of weight gain at both premenopausal and perimenopausal ages. Methods for identifying breast cancer have been described in detail by Kreger et al. (26). Briefly, breast cancer occurrences were identified by self-report, surveillance of admissions to the only local hospital, and review of the state health department's death records and the National Death Index. All documents were scrutinized to find the earliest pathology reports confirming breast cancer diagnosis in each subject, and each case was coded using the International Classification of Diseases for Oncology. All cases confirmed through the end of 1999 were available for this analysis. Breast cancer cases that occurred before the first exam with a measured weight or before age 55 were excluded from analyses.

Assessment of Other Variables in the Framingham Heart Study

The initial focus of the study, identifying the causes of heart disease, broadened into investigation of the association of many other health and lifestyle characteristics with myriad diseases. The data were collected in physician-administered examinations, laboratory tests, and self-report of health and lifestyle behaviors, and the content did not all remain consistent over exams. Measures tended to became increasingly sophisticated and numerous over time. For example, exam 1 included 78 measures that focused on a physical examination, blood pressure, and some lifestyle variables; exam 22 included over 700 variables, including mental and emotional assessment measures and many variables relating to heart discomfort, heart surgery, venous symptoms, and vascular and cerebrovascular symptoms and events. Weight at age 25 was not measured, as all women who entered the study were older than 25 yr, but was asked in exam 7. Menopausal status was queried for the "interim" period (that is, from the previous exam until that exam) in exams 2 and 4; in exam 5, "age at which menses ceased" was queried. Questions about cessation of menses were included in subsequent exams, but their content varied. Questions about type of menopause and HRT use were first included in exam 8. Alcohol and tobacco use was initially queried in exam 1 and at multiple but not all subsequent exams. Physical activity was first queried in exam 7 and again at several additional exams. Over time assessment became more specific, but not all variables were assessed at every exam.

Variable Construction

Three age periods were defined for these analyses: premenopausal (from age 25, the earliest age for which a weight was available, to 44), perimenopausal (ages 45–55), and postmenopausal (age >55). We used age-based definitions for these analyses because hormonal function declines with age, and a number of analyses examining risk factors for breast cancer, including weight, have found age 50 or 55 to be equivalent or better discriminators of risk compared with reported menopausal status (27–29).

Weight was scheduled to be measured at each exam a woman attended. If a woman did not attend an exam or was not weighed, all data from that exam were excluded from analyses. Weight at age 25 was reported by the woman at either the first or second exam, from 1948 to 1954. Weights for ages 45 and 55 were created using the weight from the closest exam within 3 yr before or after that age. Weight at all other ages was taken from the exam most closely preceding that age, up to 5 yr prior to the age. For analyses of weight gain from age 55, a woman must have had a weight measurement subsequent to the weight measurement used for age 55 to calculate a weight gain.

A high proportion of women who were later diagnosed with breast cancer had lost weight after age 55. Therefore, a second analysis of weight change after age 55 used weight at least 2 yr but less than 7 yr prior to the event to minimize the effect of any possible prediagnostic weight loss. Women missing a particular weight variable (for example, weight for age 45) were excluded only from analyses using that particular variable.

For most analyses, stable weight was defined as weight change within 2 kg in either direction, and further weight change was delimited at 5-kg intervals. Because weight change was small for the 10-yr period between ages 45 and 55, stable weight during that age interval was defined as change within 1 kg and delimited only at 2 and 5 kg.

Other variables included in analyses were height at baseline (continuous and by quintiles); age at first birth (nulliparous, <20, 20–24, 25–29, 30–34, 35+); parity (0, 1, 2, 3, 4, 5+); BMI at age 25, 45, or 55 yr (BMI calculated as kg/m², < median and ≥ median); HRT use (ever, never); cigarette smoking (current, former, never); and alcohol consumption per day (none, <5 g, 5 to <15 g, ≥15 g). The latter three variables were analyzed as time dependent.

Statistical Analyses

Follow-up began in 1948, when participants were recruited into the study. Analyses used proportional hazards models with age as the timescale and a first diagnosis of breast cancer as the event (30). Weight change, which was assessed up to the age at which an event occurred, was used as a time-varying covariate. A person with a missing value for any variable used in an analysis was excluded from that particular analysis. Observations for a woman were excluded from subsequent analyses after a report of breast cancer. Analyses assessed weight change from ages 25 to 44 yr, 45 to 55 yr, after 55 yr until age at an event, and from age 25 yr until age at an event (adult lifetime). Full models and models stratified by hormone use, BMI at start of age period, age at first birth, and age at first pregnancy, where appropriate, were examined. Data are presented only for multivariate adjustment (height, initial BMI, hormone use, age at first birth, parity, alcohol use, and smoking), age-only adjustment, and age-only stratified by hormone use. Because of the small number of cases and the lack of any evident effect of covariates in the main analyses (no 95% confidence interval [CI] for these covariates excluded 1.0), the stratified analyses did not include covariates. Trend assessment of weight gain excluded the weight loss category; weight gain was categorized as previously described, with sequential integers assigned to each increasing weight gain category.

Results

Adult weight gain was common in this sample but was less common with increasing age (Table 1). During

Table 1. Risk of Late-Onset Breast Cancer Associated With Weight Change at Selected Times: Original Framingham Cohort, 1948–1996

Weight Change (kg)	Sample With Data on All Covariates: *n* Cases	Person-Years of Follow-Up	Age-Adjusted RR	Multivariate-Adjusted RR[a]	Full Sample: *n* Cases	Person-Years of Follow-Up	Age-Adjusted RR
Adult lifetime: from age 25							
≤–5	14	4361	1.1 (0.5–2.3)	1.0 (0.5–2.2)	15	4553	1.2 (0.6–2.5)
>–5 to –2	8	2900	1.0 (0.4–2.4)	1.0 (0.4–2.4)	8	3004	1.0 (0.4–2.4)
>–2 to 2	15	5882	Reference	Reference	15	6163	Reference
>2 to 5	22	6510	1.4 (0.7–2.6)	1.4 (0.7–2.7)	22	6744	1.4 (0.7–2.6)
>5 to 10	28	10436	1.1 (0.6–2.1)	1.2 (0.6–2.2)	32	10970	1.3 (0.7–2.3)
>10 to 15	25	8614	1.2 (0.6–2.3)	1.3 (0.7–2.4)	26	9051	1.3 (0.7–2.6)
>15 to 20	23	5721	1.7 (0.9–3.2)	1.7 (0.9–3.4)	25	6035	1.8 (1.0–3.5)
>20 to 25	20	3277	2.5 (1.3–4.9)	2.6 (1.3–5.1)	21	2433	2.6 (1.4–5.1)
>25	10	3517	1.2 (0.5–2.6)	1.2 (0.5–2.7)	10	3763	1.2 (0.5–2.6)
P value for weight gain trend			0.050	0.048			0.046
Postmenopausal: from age 56							
≤–10	12	3521	1.0 (0.5–2.0)	0.9 (0.5–1.8)	13	3592	1.0 (0.5–2.0)
>–10 to –5	31	5743	1.8 (1.1–2.9)	1.7 (1.0–2.8)	31	5855	1.7 (1.1–2.8)
>–5 to –2	22	7412	1.1 (0.7–1.9)	1.1 (0.6–1.8)	24	7594	1.2 (0.7–1.9)
>–2 to 2	45	18625	Reference	Reference	48	19939	Reference
>2 to 5	27	7124	1.5 (0.9–2.4)	1.5 (0.9–2.4)	28	7277	1.5 (0.9–2.4)
>5	19	6075	1.1 (0.6–2.0)	1.1 (0.6–1.9)	19	6153	1.1 (0.6–1.9)
P value for weight gain trend			0.415	0.562			0.460
Premenopausal: age 25–44							
≤–2	5	3258	0.4 (0.2–1.8)	0.4 (0.1–1.2)	5	3305	0.4 (0.2–1.2)
>–2 to 2	16	4611	Reference	Reference	16	4636	Reference
>2 to 5	21	5633	1.1 (0.6–2.1)	1.1 (0.6–2.1)	21	5666	1.1 (0.6–2.1)
>5 to 10	32	8442	1.1 (0.6–2.0)	1.1 (0.6–1.9)	34	8676	1.4 (0.6–2.1)
>10 to 15	20	4802	1.2 (0.6–2.3)	1.2 (0.6–2.3)	21	4845	1.3 (0.7–2.4)
>15	13	4843	0.8 (0.4–1.6)	0.8 (0.4–1.6)	13	4888	0.8 (0.4–1.6)
P value for weight gain trend			0.626	0.620			0.677
Perimenopausal women: age 45–55							
≤–1	16	8224	0.5 (0.3–0.9)	0.5 (0.3–0.9)	16	8291	0.5 (0.3–0.9)
>–1 to 1	26	6557	Reference	Reference	27	6634	Reference
>1 to 2	14	2829	1.3 (0.7–2.4)	1.3 (0.7–2.5)	14	2837	1.2 (0.6–2.3)
>2 to 5	29	7559	1.0 (0.6–1.6)	1.0 (0.6–1.8)	27	7635	0.9 (0.5–1.6)
>5	23	6299	1.0 (0.6–1.7)	1.0 (0.6–1.8)	25	6366	1.1 (0.6–1.8)
P value for weight gain trend			0.803	0.921			0.891

a: RR adjusted for height, BMI at start of age period, hormone use, age at first birth, parity, alcohol use, and smoking.

premenopausal ages (25–44 yr) women gained weight 65% of the time (65% of person-years), whereas during perimenopausal (45–55 yr) and postmenopausal (>55 yr) ages women gained weight 44% and 27% of the time, respectively (44% and 27% of person-years). From early adulthood (age 25) to the end of follow-up, women gained weight 74% of the time (74% of person-years).

Lifetime adult weight gain (from age 25) was associated with an increased risk of late-onset breast cancer. Table 1 presents relative risks (RRs) for the full sample (age adjustment only) and for the smaller sample that had complete data for all covariates (height, initial BMI, hormone use, age at first birth, parity, alcohol use, and smoking adjustment). The RRs, 95% confidence limits, and *P* values for trend were similar in all three analyses (*P* trend = 0.05 for all analyses).

Weight gained during specific periods of life, that is, during premenopausal (ages 25–44), perimenopausal (ages 45–55), and postmenopausal ages (age >55), was not associated with increased risk of late-onset breast cancer. Decreases in RR estimates were observed for weight loss between ages 25 and 44 and ages 45 and 55, although the decrease was statistically significant only from ages 45–55. Adjustment for covariates did not result in any substantive changes from risks and trends found for the full sample, and none of the 95% CIs of the RR estimates for these covariates with weight gain excluded 1.0.

Table 2 presents risk associated with adult lifetime weight change (from age 25 yr) stratified by hormone use. Only 898 women, including only 50 cases, had ever used HRT in this cohort. Neither trend estimate was significant at the 0.05 level, with the generally increasing trend seen in the no-HRT-use group arrested at the largest weight gain category (RR = 0.8). The small number of cases for some weight change categories resulted in very wide CIs, particularly for the HRT-use group. The RR estimate for >20–25 kg weight gain of 2.9 (CI 1.3–6.3) for women who did not use HRT was the only statistically significant result.

Stratification by initial BMI and age at first birth did not yield risk estimates for weight gain that were substantially different from the full model (data not shown). To assess the effect of weight loss possibly associated with breast cancer, weight taken at least 2 yr prior to, rather than weight most immediately prior to, a breast cancer event was used to calculate weight gain after age 55. This removed the apparent risk associated with moderate weight loss after age 55 seen in Table 1 (RR for weight loss of 5–10 kg decreased from 1.7 [1.1–2.8] to 1.3 [0.8 – 2.2]).

Discussion

An increased risk of late-onset breast cancer was found for lifetime adult weight gain. This increase in risk was highest for weight gains of between 15 and 25 kg, with RRs of approximately two, comparable with or slightly higher than risk levels seen in both case-control and cohort studies (2,12,14,15,21,31–34). The trend was of borderline significance, influenced by the RR for the highest weight gain category (>25 kg), which arrests the generally increasing trend seen for the rest of the weight categories. This could be the result of a statistical artifact (there are only 10 cases) or a real biological effect such as a threshold. This lower RR estimate for the largest weight gain category was also seen for postmenopausal and premenopausal weight gain.

Although some of the covariates included in the full models were associated with breast cancer in our analyses, they were not associated with weight gain, and none substantially affected risk estimates. We did not include a covariate relating to physical activity because previous analyses of self-reported physical activity among women in this data set call into question its validity for women (35,36). A study of physical activity and risk of breast cancer in the Framingham study found a nonsignificant increase in risk with increasing physical activity (37), whereas a number of other studies have found an inverse association (2,38–40), which was found to vary by birth cohort (39) and sometimes was only seen in women of low or normal BMI (38,39). None looked at the interaction of weight gain and physical activity. Increased physical activity would be expected to diminish weight gain, but we cannot speculate on whether inclusion of a valid physical activity measure would have diminished the association found in our analyses. In terms of available di-

Table 2. Adult Lifetime Weight Gain From Age 25 Stratified by Use of HRT: Original Framingham Cohort, 1948–1996

	No HRT Use			Any HRT Use		
Weight Change (kg)	*n* Cases	Person-Years of Follow-Up	Age-Adjusted RR	*n* Cases	Person-Years of Follow-Up	Age-Adjusted RR
≤–2	17	5058	1.2 (0.5–2.6)	6	2264	1.0 (0.5–5.3)
>–2 to 2	10	3925	Reference	5	2044	Reference
>2 to 5	18	4261	1.7 (0.8–3.7)	4	2292	0.7 (0.2–2.6)
>5 to 10	18	7033	1.1 (0.5–2.3)	11	3508	1.3 (0.5–3.8)
>10 to 15	20	5751	1.5 (0.7–3.1)	5	2917	0.7 (0.2–2.6)
>15 to 20	14	3978	1.5 (0.7–3.5)	10	1778	2.3 (0.8–6.8)
>20 to 25	17	2391	2.9 (1.3–6.3)	4	877	1.9 (0.5–7.2)
>25	5	2734	0.8 (0.3–2.3)	5	806	2.6 (0.7–9.0)
P value for weight gain trend			0.478			0.071

etary measures, adjustment for alcohol did not alter observed associations. We did not examine other measures of diet for several reasons. The dietary measures available for this cohort were not comprehensive and focus largely on sources of fat thought to be relevant to heart disease. Given the well-documented bias in underreporting of energy with increasing BMI (41–43) and the inconsistent evidence on diet and breast cancer (44,45), it is unlikely that adjustment for the available measures of diet would have altered observed associations.

Stratification by covariates also did not yield significantly different risk estimates, but sample sizes for stratified analyses were small and CIs were wide. A larger sample would be required to assess the effect of these covariates. This was evident in the analysis stratified by HRT, for which the small numbers of cases in many of the weight change groups resulted in very wide CIs. Although the HRT results are difficult to interpret because of the limited sample size, particularly among women taking HRT, we presented the results because of strong evidence in larger, more recent cohorts that increases in breast cancer risk associated with either weight gain or obesity are either limited to or much larger among women who have never used HRT (14,15,18,20,21,31,46,47). Consistent with these findings, we observed a statistically significant and higher RR among women who had gained 20–25 kg and had not used HRT than was seen in women with the same weight gain who had used HRT. Although the sample size was small, the weight measures used in this study were measured by health professionals during physical examinations, thus eliminating the error associated with self-report of weight that may exist in other studies.

It has been suggested that timing of weight gain may be related to breast cancer risk (12,15,19,22–24). In particular, this relates to times of hormonal change, such as pregnancy, menopause, and the postmenopausal period. Mechanisms have not been clearly elaborated but include concurrent or future hyperinsulinemia and insulin resistance associated with weight gain during pregnancy and the effect of adiposity, especially central adiposity that predominates during and after menopause, on ovarian hormone metabolism and triglyceride, insulin, and IGF levels (2,5,23,24,48). Our analyses did not show any association of weight gain pre-, peri-, or postmenopausally with risk of late-onset breast cancer. However, our sample size was small to detect differences. Fewer than half of the cases first became pregnant at age 25 or later, the time of the first reported weight in this sample, and so the effect of weight specifically around the time of pregnancy could not be assessed. In addition, only a small proportion of our sample gained weight after age 55; thus, our sample was also less than ideal to study the effect of weight gain in older, and presumably postmenopausal, women.

We are unaware of any other studies that have specifically examined weight gain at pregnancy or at premenopausal (25–44 yr) or perimenopausal ages (45–55 yr) and the risk of late-onset breast cancer. Findings from two studies that looked at postmenopausal weight gain were equivocal. One noted an increased but nonsignificant risk but did not present data (15); in the other, an increased risk was observed only in some subgroups of women (19). Interest in timing of weight gain, potential mechanisms for an association, and the continued increase in obesity and adult weight gain in the United States and other industrialized countries (49) suggest that the association of timing of weight gain and breast cancer risk continues to be an area of research need despite the null findings of these analyses. This might better be explored in a more contemporary cohort in which weight gain is more common than in the original Framingham cohort, which covered a period from the 1950s through 1980s, during which time BMIs for the U.S. population were relatively stable (49).

Data on the association of weight loss and risk of late-onset or postmenopausal breast cancer are limited (2). The suggestion here of a decreased RR of late-onset breast cancer for weight loss from ages 25 to 44 and 45 to 55 is new and requires confirmation in other studies. One other study of postmenopausal women found a significantly decreased risk for weight loss from age 18 to interview, with the strongest effect seen in women less than 10 yr past menopause (46). However, one of the largest cohort studies found no association between weight loss and breast cancer risk (15). Three smaller studies of postmenopausal or mainly postmenopausal women also found no association between weight loss and breast cancer risk, with slightly increased but nonsignificant risks reported (13,16,19). However, some of this effect may have been due to prediagnostic weight loss. One of these studies found that the increased risk changed to a nonsignificant decreased risk for women who had lost weight over a prolonged interval (20 yr or more) before the diagnosis of breast cancer (13). Another study, which had found no overall association with weight loss after age 45, found a significantly decreased risk for women whose maximum weight occurred before age 45 (21). Because weight loss in these subgroups of women occurred so long prior to diagnosis of breast cancer, it is unlikely that the weight loss would have been related to preclinical breast cancer. In addition, a study that found no effect of weight loss on postmenopausal breast cancer risk overall noted a significantly decreased risk when weight loss was combined with frequent physical activity (50). These limited data on weight loss and breast cancer risk suggest that further study is warranted, but it will be important to determine the cause of weight loss before even tentative conclusions can be made.

The Framingham data have a number of strengths for looking at the association between weight gain and late-onset breast cancer. The anthropometric data were collected during a physical examination by a health professional at each exam, with approximate intervals of 2 yr between exams, thus providing reliable and frequent measurements that continued up to the time of a breast cancer diagnosis. Many covariates are also collected at intervals, although not always every 2 yr, and thus are available for approximately the time of diagnosis as well as for earlier periods of interest. Because the study began over 50 yr ago, most of the female participants are now postmenopausal. Nearly all cases of breast cancer were confirmed by histological reports, and breast cancer occurrence in the Framingham study is not statistically different from the rates found in the Connecticut Surveillance, Epidemiology, and End Results program (26). Thus, it is believed that virtually all clinically detected incident cases of breast cancer were ascertained (26,51).

However, this data set also has a number of limitations in assessing the association between weight gain and breast cancer. The number of participants in the study was small relative to some contemporary cohorts, thereby limiting our ability to find an association. Weight gain was far less common than in contemporary cohorts, limiting our ability to investigate pre-, peri-, and postmenopausal weight gain. Use of HRT, which has been important in the association of weight and breast cancer in other studies (14,15,18,20,21,31,46,47), was not as common in this cohort as more recent cohorts, and the relatively small Framingham sample prevented clear interpretation of analyses stratified by use of HRT. A reliable assessment of timing and type of menopause was not available, resulting in possible misclassification of menopausal status and inability to examine the association by type of menopause. However, Morabia and Flandre conclude that misclassification bias can result from both menses- and age-based classifications of menopause (29). Despite these limitations, this analysis may prompt other investigators to examine these associations in larger and more contemporary cohorts.

In summary, lifetime adult weight gain was associated with an increased risk of late-onset breast cancer. These data support current recommendations to avoid adult weight gain. No specific period of adult weight gain was associated with risk. Because biological mechanisms suggesting that weight gain at hormonally important times could be related to breast cancer risk, studies with larger numbers of breast cancer events in more current populations, among whom weight gain even in postmenopausal women would be expected, should continue to explore these associations.

Acknowledgments and Notes

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